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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ZARA, JANE J	

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1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/561,691	KAZAKOV ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15,18 and 22-29* is/are pending in the application.

4a) Of the above claim(s) *22-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Seq. Compliance Notice*.

DETAILED ACTION

This Office action is in response to the communication filed 7-15-08.

Claims 1-15, 18, 22-29 are pending in the instant application.

Election/Restrictions

Claims 16, 17, 19-21 and 30-33, which have been canceled by amendment, and claims 22-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 7-15-08.

Applicant's election of Group I, claims 1-15 and 18, in the reply filed on 7-15-08 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures. The sequences listed in, *e.g.*, Figures 3, 6, 8, 9A,

14, 18, 20, 21 and 22 must be accompanied by an appropriate SEQ ID NO. (See the accompanying *Notice to Comply*).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-15 and 18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to complexes and polynucleotides capable of binding to, and partially complementary to, a sequence of any target, which complexes and polynucleotides also comprise a catalytic domain capable of catalytic activity, and a regulatory nucleic acid sequence that also binds to at least a portion of the target binding sequence, which regulatory sequence inhibits the catalytic activity in the absence of binding between the target binding sequence and a target molecule, and which polynucleotides specifically bind to any target nucleic acid molecule and circularize as a result of target binding.

The specification and claims do not adequately describe the concise structural features comprising this broad genus of polynucleotides or complexes, wherein binding

occurs faithfully between any target binding sequence and its partially complementary target, and wherein circularization occurs upon binding to the target sequence, and wherein any regulatory sequence successfully inhibits catalytic activity of a catalytic domain in the absence of target sequence binding. The specification teaches a series of Lassos with varying abilities to be allosterically regulated, a subset of which undergo target-dependent circularization (see, *e.g.*, pages 42-49 or the specification). Six Lassos were constructed comprising between 5-10 base pairs to the complement of (murine) TNF-α, and comprising between 5-6 base-pair regulatory sequences. The Lassos, however, were found to vary widely in their abilities to undergo allosteric regulation upon binding to the fully complementary sequence, at times requiring 20% formamide in the reaction buffer for enhancing successful self-processing, and requiring varying lengths of regulatory sequences, as well as varying lengths of target binding sequences and target sequences available for target binding efficiency and/or target-dependent processing. In addition, some polynucleotide constructs (Lassos) underwent circularization in the absence of target sequences.

It is unclear, therefore, from the broad genus of compounds claimed, what *portion* of the target binding sequence is required to exactly complement the target gene for achieving the functions claimed, what regulatory sequences are required for achieving circularization in the presence of the proper target sequence, and what concise structural features must be present for providing generally for the functions claimed, of being capable of binding to partially complementary sequences of any target, of having a catalytic domain capable of catalytic activity in the presence of target

binding sequences, and of having a functional regulatory nucleic acid sequence that binds to at least a portion of any target binding sequence, but inhibits the catalytic activity of the catalytic domain in the absence of binding between the target binding sequence and the target molecule - whereby the polynucleotides specifically bind to any target nucleic acid molecule and circularize as a result of target binding.

One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the broad genus of compounds claimed which provide for the functions claimed. Thus, Applicant was not in possession of the claimed genus. One of skill in the art would reasonably conclude that adequate written description is lacking for the instantly claimed genus of polynucleotides and complexes.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4, 6-15, and 18 are rejected under 35 U.S.C. 102(e) as being anticipated by Stanton et al (US 7,125,660).

Stanton et al (US 7,125,660) teach polynucleotides which are optionally synthetically prepared or expressed from an expression construct, and are comprised of

either DNA, RNA, or analogs thereof, and which polynucleotides specifically bind to a target molecule which is optionally RNA or DNA, comprise a catalytic domain which is a ligase catalytic domain obtained from a hairpin ribozyme, and further comprise a regulatory nucleic acid sequence that binds to a portion of the target binding sequence, and inhibits catalytic activity in the absence of target sequence binding by the target binding sequence portion of the polynucleotide, wherein the ligase topologically links the polynucleotide to the target sequence via the 5' and 3' termini of the polynucleotide, thereby circularizing the polynucleotide around the target sequence in vitro (see esp. the abstract; col. 1-9; 18-20; 39; claims 1-4, 7-10).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-15 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stanton et al (US 7,125,660), Stanton et al (US 2003/0087239), and Lizardi et al (USPN 5,312,728), the combination in view of Wu (WO 03/023049).

The claims are drawn to complexes and polynucleotides capable of binding to and partially complementary to a target sequence, also comprising a catalytic domain capable of catalytic activity which is optionally ligase activity, and a regulatory nucleic acid sequence that binds to at least a portion of a target binding sequence, which regulatory sequence inhibits catalytic activity in the absence of binding between the target binding sequence and the target molecule, and which polynucleotides specifically bind to a target nucleic acid molecule and circularize as a result of target binding.

Stanton et al (US 7,125,660) teach polynucleotides which are optionally synthetically prepared or expressed from an expression construct and are comprised of either DNA, RNA, or analogs thereof, and which polynucleotides specifically bind to a target molecule which is optionally RNA or DNA, comprise a catalytic domain which is a ligase catalytic domain obtained from a hairpin ribozyme, and further comprise a regulatory nucleic acid sequence that binds to a portion of the target binding sequence, and inhibits catalytic activity in the absence of target sequence binding by the target binding sequence portion of the polynucleotide, wherein the ligase topologically links the polynucleotide to the target sequence via the 5' and 3' termini of the polynucleotide,

thereby circularizing the polynucleotide around the target sequence in vitro (see esp. the abstract; col. 1-9; 18-20; 39; Figures 38, 39A, 73; claims 1-4, 7-10).

Stanton et al (US 2003/0087239) teach diagnostic applications comprising biosensors which comprise polynucleotides that recognize and bind to target molecules, which binding between the target binding region of the biosensor polynucleotide and the target molecule trigger a conformational change in the polynucleotide, optionally triggering catalytic activity which is ligase activity, wherein ligation occurs between the target activation site of the polynucleotide containing biosensor construct, and a nucleotide which couples to at least one signaling moiety via a ligation reaction, causing a change in the optical properties of the signaling moiety upon ligation (see the abstract; pages 1-3; page 4 at paragraph 0043 - page 7 at paragraph 0080; page 8 at 0090; page 9 at 0097; page 10 at p0109; Figures 2 and 3; claims 1-9).

Lizardi et al (USPN 5,312,728) teach polynucleotide molecular switches comprising a probe sequence for detecting nucleic acid target sequence binding or detecting hybridization with a target sequence by the molecular switch, which switch undergoes a conformational change upon target sequence binding, and wherein a detectable signal is caused by an allosteric change in the molecular switch, indicating target sequence hybridization by the polynucleotide molecular switch, and wherein in the inactive state (*i.e.* prior to the conformational change) the molecular switch binds to a regulatory region of the switch (see the abstract; col. 4-7; Figures 1-13; claims 1, 7, and 15-18).

The primary references of Stanton et al, Stanton et al and Lizardi et al do not teach the circularization of polynucleotides via 5' and 2' hydroxyl groups using an internal nucleotide of a polynucleotide.

Wu (WO 03/023049) teaches the routine use of commercially available ligases used to ligate the 5' end of a polynucleotide to the 2' hydroxyl group of an internal nucleotide of a polynucleotide for enrichment of molecules having free 5' phosphates (see pages 4-5, esp. at 0010 and 0011).

It would have been obvious to one of ordinary skill in the art to design polynucleotides that act as biosensors and that specifically bind to a target molecule which is optionally RNA or DNA, comprise a catalytic domain which is a ligase catalytic domain obtained from a hairpin ribozyme, and further comprise a regulatory nucleic acid sequence that binds to a portion of the target binding sequence and inhibits catalytic activity in the absence of target sequence binding by the target binding sequence portion of the polynucleotide, because Stanton and Stanton teach the design of biosensors that are allosterically regulated and circularize in the presence of target sequences, and Lizard teaches the motivation to use allosteric biosensors with increased sensitivity in biological solutions. One of ordinary skill in the art would have reasonably expected that, using the teachings of biosensor construction taught previously by Stanton, Stanton and Lizardi, that the ligase of the biosensor topologically links the polynucleotide of the biosensor to a complementary target sequence via the 5' and 3' termini of the polynucleotide, thereby circularizing the polynucleotide around the target sequence in vitro, because this result had been obtained in vitro by Stanton and

Stanton. One of ordinary skill in the art would also have reasonably expected that a ligase component of the biosensor would optionally include a ligase that utilizes either a 5'- 2' linkage or a 5' - 3' because both ligases were well known in the art at the time of the instant invention to be modular domains, and ligase had been used successfully to circularize polynucleotides using the biosensors previously taught by Stanton and Stanton.

One would have motivated to design and use polynucleotide biosensors having allosteric catalytic properties because Stanton, Stanton and Lizardi teach the advantages of using allosteric catalytic biosensors to improve the sensitivity in detecting target sequences in biological solutions as a diagnostic assay. One would have expected that generating circular products via a ligase would provide for products that are easily detectable and discernable from linear (*i.e.* non-circularized) nucleic acid products, thereby improving the sensitivity of detecting target sequences using the instantly claimed allosteric biosensor molecules.

One would have been motivated to utilize ligases that link 2' and 3' hydroxyls with 5' phosphates because the use of either ligase reactions allows for increasing the circular reaction products, leading to enhanced sensitivity and detection of target sequences, and the use of biosensors that include regulatory sequences that prevent catalytic activity in the absence of target sequences provides for a reduction in non-specific reaction products, reducing background reaction products, and increasing the sensitivity of assays for detecting the presence of target sequences. One would have been motivated to use ligases that link internally to polynucleotides (e.g. via the 2'

hydroxyl groups of the nucleotides within the polynucleotide) because this allows for more available substrates for circularized products, thereby amplifying the desired reaction products and enhancing assay sensitivity.

Therefore, the instant invention would have been obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz, can be reached on (571) 272-0763. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
9-2-08

/Jane Zara/

Primary Examiner, Art Unit 1635